	G-V		Steady-State Inactivation	
	$V_{0.5}$	k	$V_{0.5}$	k
$Na_V1.4$	-23.5 ± 0.8 (8)	3.1 ± 0.2	-46.4 ± 1.1 (9)	4.3 ± 0.4
1579 TAG + Phe	-21.8 ± 0.9 (9)	3.4 ± 0.6	-46.4 ± 0.7 (9)	5.3 ± 0.3
1579 TAG + 3-F_1-Phe	-21.0 ± 0.9 (9)	3.8 ± 0.5	-46.6 ± 0.9 (9)	5.1 ± 0.4
1579 TAG + 3,5-F_2-Phe	-19.8 ± 1.0 (7)	3.5 ± 0.4	-44.0 ± 0.8 (7)	5.6 ± 0.4
1579 TAG + 3,4,5-F_3-Phe	-23.0 ± 0.8 (10)	3.1 ± 0.2	-43.0 ± 0.6 (9)	5.3 ± 0.2
1579 TAG + Cha	-23.2 ± 0.6 (9)	3.2 ± 0.2	-42.8 ± 1.0 (4)	5.5 ± 0.3
1586TAG + Phe	-22.8 ± 0.5 (11)	3.6 ± 0.2	-46.9 ± 1.9 (5)	4.4 ± 0.7
1586TAG + 3-F_1-Phe	-21.0 ± 0.7 (9)	4.1 ± 0.2	-46.9 ± 0.7 (6)	4.6 ± 0.9
1586TAG + 3,5-F_2-Phe	-25.6 ± 0.7 (5)	3.2 ± 0.2	-49.8 ± 0.7 (4)	4.1 ± 0.2
1586TAG + 3,4,5-F_3-Phe	-24.5 ± 0.7 (5)	4.0 ± 0.6	-47.9 ± 2.0 (4)	4.6 ± 0.6
1586TAG + Cha	-26.9 ± 0.6 (5)	4.9 ± 0.2	-49.1 ± 1.7 (5)	5.4 ± 0.4

Table S1. Boltzmann fits of normalized activation (Fig. 2B) and steady-state inactivation (Fig. 2C) for wild-type and mutant channels. Number of cells indicated in parentheses. The normalized currents were fit by $I(V)/I_{max} = 1/(1+e^{(V-V_{0.5})/k})$, where V is membrane potential, $V_{0.5}$ is the midpoint, and k is a slope factor. Perfusion of oocytes expressing wild-type $Na_V1.4$ with 200 μM lidocaine resulted in a ~8-mV hyperpolarizing shift in the $V_{0.5}$ of steady-state inactivation from -46.0±0.6 to -53.5±1.6 mV (P=0.006, t-test). This lidocaine-induced shift was eliminated in the trifluorinated mutant 3,4,5-F_3-Phe1579, -43.0±0.6 vs. -45.0±1.4 mV (P=0.24), for control and lidocaine saline, respectively. No such relief was seen when 3,4,5-F_3-Phe was incorporated at the 1586 position as 200 μM lidocaine exposure resulted in a ~7-mV hyperpolarizing shift, $V_{0.5}$ = -46.0±1.2 vs. -53.4±1.5 mV (P=0.02), for control and 200 μM lidocaine saline, respectively.

Figure S1. Cation-π influence on use-dependent inhibition at a low concentration (20 μM) of lidocaine. Lidocaine was applied 5 min before high-frequency stimulation. Tonic inhibition was negligible at this low concentration. A-B, Representative currents at -10 mV for 100 10-ms depolarizations from a holding potential of -100 mV, every 10^{th} trace shown for clarity. Stimulation rate was either 20 Hz (A) or 50 Hz (B). Currents were stable at 50 Hz in the absence of lidocaine. Left panels are wild-type, right panels are for 3,4,5-F_3-Phe1579. C, Fraction of control (P_{100}/P_1) after 100 depolarizations for 5 wild-type and 3 mutant oocytes. Two asterisks indicate $P<0.005$.

Supplemental Figure 1